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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Application Number: 09/996,484
Filing Date: November 28, 2001
Appellant(s): CHOO ET AL.

Dahna S. Pasternak
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 4/1/2009 appealing from the Office action mailed 6/4/2008.

This examiner's answer vacates the examiner's answer mailed 6/10/2009. This examiner's answer changes the headings; these changes address only clerical issues that were inadvertently omitted in the previous examiner's answer.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is substantially correct. The changes are as follows:

WITHDRAWN REJECTIONS

The following grounds of rejection are not presented for review on appeal because they have been withdrawn by the examiner.

A. The rejection of claims 34 and 48 under 35 U.S.C. 112, first paragraph, was withdrawn in the advisory action mailed 4/28/2009.

B. The rejection of claims 34 and 48 under 35 U.S.C. 112, second paragraph, was withdrawn in the advisory action mailed 4/28/2009.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

WO 96/06110	GILMAN et al.	2-1996

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 34 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gilman et al. WO 96/06110.

Claim 34 is directed to a complex comprising a heterodimer comprising a first and second polypeptide, wherein the first and second polypeptides bind to DNA and the first or second polypeptide comprises an engineered, non-naturally occurring Cys2-His2 zinc finger binding domain, and a ligand that binds to the first and second polypeptides and mediates heterodimerization of the first and second polypeptides.

Claim 48 is directed to a switching system comprising a first and second polypeptide and a ligand in which the first polypeptide binds to the second polypeptide to form a heterodimer and the binding of the first and second polypeptides is mediated by binding the ligand to the first and second polypeptides, wherein the first and second polypeptides bind to DNA and the first or second polypeptide comprises an engineered Cys2-His2 zinc finger DNA binding domain.

Gilman et al. teaches composite DNA-binding proteins in which two or more heterologous DNA-binding domains are linked together through an association mediated by a multimerizing agent. (See, e.g., page 2, lines 9-13; page 3, lines 1-6; and page 8, lines 9-19.) Gilman et al. teaches that the multimerizer-linked composite DNA-binding proteins comprise two or more chimeric proteins, each comprising at least one binding site for a multimerizing ligand and at least one component DNA-binding domain. (See especially the first full paragraph on page 5.) Thus, Gilman et al. teaches a complex or switching system comprising first and second proteins and a ligand (i.e., multimerizing agent), wherein the ligand binds to both the first

and second polypeptides such that the first and second polypeptides are joined to form a heterodimer (i.e., the polypeptides comprise, at least, heterologous DNA binding domains).

Gilman et al. further teaches Cys2-His2 zinc finger DNA binding domains as one of a small number of explicitly named classes of DNA binding domains that might be comprised by the composite DNA-binding proteins. In addition, Gilman et al. teaches that the zinc finger DNA-binding domains can be engineered by mutagenesis to provide a DNA-binding domain having decreased, increased or altered recognition specificity of DNA binding. (See especially the first full paragraph on page 10.)

Although Gilman et al. does not explicitly teach that the engineered Cys2-His-2 zinc finger binding domain should not occur in nature and, as described above, it would be impossible to know whether any given engineered binding domain occurs in nature, Gilman et al. does teach that the engineered DNA binding domains might be selected from phage display libraries (see especially page 10, lines 13-15), which would comprise large numbers of random mutants. As it is reasonable to expect that at least some of the DNA binding domains selected in that manner would be non-naturally occurring, the inclusion of a non-naturally occurring engineered Cys2-His-2 zinc finger binding domain in the complex of Gilman et al. would have been obvious to one of ordinary skill in the art at the time the invention was made because one would be motivated to use any DNA binding domain having increased affinity or altered specificity as contemplated by Gilman et al. Absent evidence to the contrary one would have a reasonable expectation of success in obtaining a non-naturally occurring engineered Cys2-His2 zinc finger binding domain by the method of phage display because it is routine in the art to isolate peptides

having desirable properties, such as altered DNA binding affinity or specificity, by the process of phage display.

In view of the foregoing, the complex and switching system of the instant claims 34 and 48, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC § 103(a) as obvious over the art.

(10) Response to Argument

With respect to the rejection of claims 34 and 48 under 35 U.S.C. 103(a) as being unpatentable over Gilman et al. WO 96/06110, Appellant's arguments filed 4/1/2009 have been fully considered but they are not persuasive.

Claim 34 is directed to a complex comprising a heterodimer comprising a first and second polypeptide, wherein the first and second polypeptides bind to DNA and the first or second polypeptide comprises an engineered, non-naturally occurring Cys2-His2 zinc finger binding domain, and a ligand that binds to the first and second polypeptides and mediates heterodimerization of the first and second polypeptides.

Claim 48 is directed to a switching system comprising a first and second polypeptide and a ligand in which the first polypeptide binds to the second polypeptide to form a heterodimer and the binding of the first and second polypeptides is mediated by binding the ligand to the first and second polypeptides, wherein the first and second polypeptides bind to DNA and the first or second polypeptide comprises an engineered Cys2-His2 zinc finger DNA binding domain.

The specification defines the term "a non-naturally occurring binding domain" to mean that "the binding domain does not occur in nature, even as part of a larger molecule, and has

been obtained by deliberate mutagenesis procedures or *de novo* design techniques." See page 3, lines 29-32.

Appellant asserts that Gilman fails to teach or suggest anything about engineered zinc finger proteins in addition to failing to teach anything about non-naturally occurring Cys2-His2 zinc finger binding domains. Appellant asserts that the rejection cannot be sustained if the term "non-naturally occurring" as applied to Cys2-His2 zinc finger domains is properly interpreted in the context of the claim.

This argument is not found persuasive. Gilman et al teach that suitable component DNA binding domains include naturally occurring zinc fingers of the C2H2 (i.e., Cys2-His2) class (e.g., page 5, lines 14-16 and 27-35). However, the teachings of Gilman et al are not limited to naturally occurring Cys2-His2 zinc finger domains. Gilman et al teach that an existing Cys2-His2 DNA binding domain can be modified, or engineered, to decrease, increase or change the recognition specificity of DNA binding (e.g., page 10, lines 4-6). Specifically, Gilman et al teach that in zinc fingers, substitutions can be made at selected positions in the DNA recognition helix (e.g., page 10, lines 11-13). Thus, Gilman et al teach the application of deliberate mutagenesis procedures to create a non-naturally occurring zinc finger sequence that has been designed to bind a particular target sequence (e.g., page 1, lines 12-15; page 10, lines 4-15). The mutagenized naturally occurring zinc finger of Gilman et al is consistent with the definition of "non-naturally occurring" provided in the instant specification. Accordingly, Gilman et al do teach engineered zinc finger proteins that are non-naturally occurring Cys2-His2 zinc finger binding domains.

Appellant asserts that Gilman fails to teach, suggest or enable complexes as claimed in which heterodimerization of first and second DNA binding domains is mediated by a ligand that binds to the DNA binding domains. The response notes that Gilman teaches fusion proteins comprising a DNA binding domain and immunophilin ligand-binding domain.

These arguments are not found persuasive. The instant claims do not require the ligand to bind directly to the DNA binding domain as suggested by Applicant. Rather, the claims only require the ligand to bind the first polypeptide and second polypeptide, where each polypeptide comprises a DNA binding domain. The claims do not prohibit the inclusion of a second domain in each polypeptide where the additional domain binds the ligand. Thus, the DNA binding domain and immunophilin ligand-binding domain fusions of Gilman et al read on the first and second polypeptide of the rejected claims.

Appellant notes that Gilman teaches the covalent linkage of DNA binding domains. Further, Appellant notes that Gilman only exemplifies DNA binding domains that have been covalently linked. Appellant asserts that Gilman does not teach or suggest the claimed complexes in which the ligand mediates heterodimerization by binding to the DNA-binding polypeptide.

These arguments are not found persuasive. Although Gilman et al do teach the covalent linkage of DNA binding domains, the reference is available as prior art for all that it teaches. At the paragraph bridging pages 2-3, Gilman et al state the following:

> It bears repeating, and should be kept in mind by the reader, that the composite DNA binding protein in certain embodiments is a single chimeric protein containing multiple and covalently-linked copies of one or more DNA-binding domains, while in other embodiments the composite DNA-binding protein comprises two (or more) "subunits", each of which is a chimeric protein in its own right containing at least one DNA-binding domain. In the latter case, the

> composite DNA-binding protein comprises two or more such subunits in a multimerizer-mediated association.

Thus, it is clear that Gilman et al teach two polypeptide subunits, where each subunit comprises a DNA binding domain, and the DNA binding domains are brought together by a ligand in what Gilman et al call multimerizer-mediated association. Gilman et al teach the multimerization of at least two chimeric proteins, each comprising at least one binding site for a multimerizing ligand, and at least one component DNA binding domain, such as a modified Cys2-His2 zinc finger, where the DNA binding domains are brought together in a complex by the ligand (e.g., page 5, lines 4-12; page 7, lines 29-31; sentence bridging pages 7-8). Gilman state, "the transcriptional activation domain may be present on a chimeric protein which further contains one or more component DNA-binding domains, which is capable of dimerizing, in the presence of a dimerizing agent, with another chimeric protein of this invention bearing a ligand-binding domain and one or more additional component DNA-binding domains." Furthermore, Gilman et al teach that the design of chimeric proteins comprising ligand binding sites capable of ligand-mediated multimerization was known in the art (e.g., page 5, lines 8-12; page 8, lines 9-19). Thus, Gilman et al do teach the claimed complexes in which the ligand mediates heterodimerization by binding to the polypeptide comprising the DNA binding domain as claimed.

Appellant asserts that the Gilman reference does not place the public in possession of ligand-mediated heterodimeric complexes as claimed. Appellant asserts that Gilman only discloses covalent linkage of DNA binding domains.

This argument is not found persuasive. Gilman teaches the ligand-mediated association of DNA binding domains in addition to covalent association. See the discussion above. Gilman et al teach each element of the claimed invention and placed the public in possession of the presently claimed invention.

In response to the *prima facie* rejection of record, Appellant has not provided objective evidence of nonobviousness, either submitted in the specification as originally filed or in reply to the rejection of record.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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